22. The set of claim 20 wherein said oligonucleotide has at least one nuclease-resistant linkage.

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23. The set of claim 20 wherein said fluorophore is a fluorescein.

24. The set of claim 20 wherein M is a mobility modifier consisting of from 2 to 100 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron.

REMARKS

Claims 1-15 have been cancelled and new claims 16-24 have been added. Claims 16-24 are currently pending in the application. All pending claims are set forth in Exhibit A with amendments shown (if applicable).

Attorney for Applicants gratefully acknowledges the interview with the Examiner on 12 July 2002 in which the proposed new claims and rejections were discussed. The new claims have been submitted to more clearly describe Applicants' invention and to overcome rejections based on 35 U.S.C. 112 second paragraph.

Basis new claims are as follows:

Table 1. Basis for New Claims

New Claim(s)	Term/Phrase	Basis
16	"(D, M)-N-T"	Claim 1
16	"(D, M)-N is an e-tag reporter"	Claims 2 & 3.
16	"1 to 500 atoms" in reference to M.	Page 17, line 28.
16	"group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron" in reference to M.	Page 14, line 43, to page 15, line 26. Page 17, lines 27-41.
16	"12 to 60 nucleotides" in reference to T.	Page 41, lines 33-35.
16	"distinct charge/mass ratio" in reference to e-tag reporters.	Page 62, lines 28-31.
16	"so that e-tag reporters of the plurality of electrophoretic probes form distinct peaks upon electrophoretic separation"	Page 5, lines 40-42, & Fig. 8. Page 6, lines 30-31, & Fig. 22. Page 6, lines 32-35, & Fig. 22A-E & G. Page 6, lines 36-37, & Fig. 24. Page 6, lines 38-44, & Fig. 25A-D. Page 7, lines 1-5, & Figs. 26 & 27.
16	"capture ligand"	Claim 1.
17	"5 to 100" in reference to the plurality of nucleotide sequences.	Claim 8. Page 8, line 35.
17	"1 to 300 atoms" in reference to M.	Page 17, line 28.

18	"charge/mass ratio in the range of –0.001 to 0.5"	Claim 8.
19	"D is a fluorophore, chromophore, or an electrochemical label."	Claim 12.
20	"formula is D-M-N-T"	Claim 2.
21	"capture ligand is biotin"	Claim 5.
22	"said oligonucleotide has at least one nuclease-resistant linkage"	Claim 1.
23	"fluorophore is a fluorescein"	Fig. 6.
24	"M is a mobility modifier consisting of from 2 to 100 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron."	Page 17, line 28.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

Provisional Double Patenting

The Examiner made the following provisional rejections under the doctrine of obviousness-type double patenting: (i) claims 1-7 as being obvious over claims 1-3, 5-7, and 9-10 of copending application Ser. No. 09/824,905; (ii) claims 1-15 as being obvious over claims 1-19 of copending application Ser. No. 09/825,245; and (iii) claims 1-5 as being obvious over claims 1-4 of copending application Ser. No. 09/824,851 and claims 1-4 of copending application Ser. No. 09/824,861.

Applicants respectfully disagree with this provisional rejection as it applies to copending applications Ser. Nos. 09/824,851 and 09/824,861, particularly in view of the amendments. The cited claims in copending applications '861 and '851 are directed to kits and compositions, respectively, of general electrophoretic probes used to detect general any ligand-antiligand binding event. The present application is directed to electrophoretic probes comprising only oligonucleotides.

In order to expedite the prosecution of this application, Applicants have enclosed appropriate Terminal Disclaimers with respect to the above copending applications to overcome the above rejections. Accordingly, Applicants respectfully request that the above rejections be withdrawn.

Objection to Claim

The Examiner objected to claims 1-15 because of typographical errors in the symbol "U_1."

Applicants respectfully submit that the new claims have obviated this objection by removing the symbol. Accordingly, Applicants respectfully request that the objection be withdrawn.

Rejections Under 35 U.S.C. 112

The Examiner rejected claims 1-15 under 35 U.S.C. 112 second paragraph because of various phrases and terms thought to be vague or confusing.

Applicants respectfully disagree with these rejections, particularly in view of the above amendments. Each instance of vague or confusing language was discussed by Attorney for Applicants and the Examiner in the interview of 12 July 2002 and it was agreed that the language of the pending claims overcomes the rejections based on 112 second paragraph. Accordingly, Applicants request that the rejections by withdrawn.

Rejection Under 35 U.S.C. 102

The Examiner rejected claims 1-3 and 10-15 under 35 U.S.C. 102(b) as being anticipated by Grossman (5,470,705). The Examiner argues as follows: Grossman discloses oligonucleotide binding compounds having polymeric tails that can be electrophoretically separated to permit multiplexed measurements. Grossman does not explicitly show a "capture ligand" on his probe compounds; however, probe capture is shown inherently by the hybridization of probes to a target polynucleotide, for example, as shown in Fig. 20B.

Applicants respectfully disagree. First, Applicants' capture ligand is not an inherent part of an oligonucleotide probe that operates by specific hybridization, as suggested by the Examiner's argument. It is a distinct moiety attached to one of the nucleotides of the probe for the specific purpose of removing from electrophoretic analysis those probes that are not cleaved (i.e. those probes that do not release an electrophoretic tag, or "e-tag reporter"). Figure 26 and 27 of the application show the result of using such a capture ligand: The same analysis was carried out in two experiments. In one experiment, uncleaved probe was not removed by capture ligands (results shown in Fig. 26), and in the other experiment, uncleaved probe was removed by capture ligands (results shown in Fig. 27). A remarkable improvement in signal can be seen that results from the use of the capture ligand to remove uncleaved probe. Not only does Grossman not disclose the distinct element of a "capture ligand," but neither does Grossman teach the function, or even the desirability of the function, of Applicants' capture ligand.

Second, the "inherent" capture in Grossman is by a different mechanism (specific hybridization) and for a different purpose than Applicants' use of a capture ligand. In Grossman, there are two "capture" events shown in Fig. 20B. The first is capture of the probe by its hybridization to a target polynucleotide. The second is capture of the target polynucleotide by its hybridization to a oligonucleotide attached to a solid phase support. The purpose of the first "capture" is to detect the presence or absence of a target sequence, and the purpose of the second is (i) to reduce the complexity of a hybridization reaction by isolating a subset of target polynucleotides, and/or (ii) to permit non-hybridizing probe to be washed away. Neither purpose relates to Applicants' use of a capture ligand, which is to remove uncleaved probe prior to electrophoretic analysis.

Accordingly, Applicants submit that the equivalent of the capture ligand in Applicants' invention is not disclosed identically in Grossman, and respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejections Under 35 U.S.C. 103

The Examiner rejected claim 5 under 35 U.S.C. 103(a) as being unpatentable over Grossman (5,470,705) in view of Babon (5,851,770). The Examiner applies Grossman as described above. Babon discloses use of a capture ligand, such as biotin, to capture on a solid phase support various hetero- and homoduplexes that may or may not contain mismatched basepairs. Captured duplexes are treated with a mismatch-recognizing nuclease that cleaves the captured sequences at mismatch locations to release fragments which are then analyzed by electrophoresis. The Examiner argues that it would be obvious to one of ordinary skill to modify the probes of Grossman to include the capture ligands of Babon, thereby obtaining Applicants' invention. One of ordinary skill would be motivated to make such a combination because of the advantages of being able to wash away unbound probe in the solid phase system disclosed by Babon.

Applicants respectfully disagree. First, the capture ligand disclosed by Babon (like Grossman) is attached to a target sequence, not a probe, and it is the target sequence that is cleaved in Babon, not a probe. This is in contrast to Applicants' invention where the capture ligand is attached to probes, and the probes are cleaved to release eTag reporters. Second, Grossman and Babon neither disclose nor suggest the desirability of placing a capture ligand on the probe, as described by Applicants. In this regard, Applicants direct the Examiner to Figs. 26 and 27 of the application which show the dramatic improvement in signal that occurs by use of a capture ligand

on the probe, as discussed above. There is no equivalent observation, or other suggestion, in either Grossman or Babon that would motivate one of ordinary skill to place the capture ligand of Babon on the probes of Grossman. Applicant submit that the combination of Grossman and Babon would not lead one of ordinary skill to Applicants' invention without an independent inventive contribution, and accordingly respectfully request that the rejection be withdrawn.

The Examiner rejected claim 4 under 35 U.S.C. 103(a) as being unpatentable over Grossman in view of Huie (5,470,967). The Examiner applies Grossman as above and cites Huie for the disclosure of "nuclease-resistant" linkages in oligonucleotides. The Examiner argues that it would have been obvious to one of ordinary skill to introduce nuclease-resistant linkages into the probes of Grossman using the teaching of Huie.

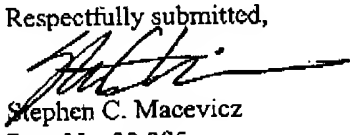
Applicants respectfully disagree. Neither Grossman nor Huie teach or suggest the analytical problem created by using a nuclease to cleave a probe. A nuclease does not always cleave every probe at precisely the same inter-nucleoside linkage, as is illustrated diagrammatically in Figure 3A-C of the application. As a result, such cleavage can give rise to spurious peaks upon electrophoretic separation. There is no suggestion or appreciation of this problem in either reference. In particular, Huie is concerned with the use of nuclease resistant oligonucleotides for therapeutic purposes; thus, the application of such compounds in analytical applications is simply not disclosed or suggested. Likewise, the thrust of Grossman is the use of ligation to modify probes for separation. The mention of nuclease modified probes is only a minor aspect of the Grossman invention[1]; thus, potential applications of nuclease-resistant oligonucleotides is not disclosed or suggested. Therefore, Applicants submit that one of ordinary skill would not be motivated to combine the respective teachings and obtain Applicants' invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

1. Several probe modification schemes are disclosed by Grossman, including ligation (Figs. 7A-D, 9, 10A-C, 18A-B; col. 12 (line 61) to col. 16 (line 53); and Examples 7 and 8), probe extension (col. 18 (line 56) to col. 19 (line 21); no example), and fragment cleavage (col. 19 (line 22) to col. 20 (line 44); no example). By the number of words and figures devoted to each, clearly ligation is the primary focus of Grossman's probe modification.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **50-2266.**

Respectfully submitted,



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Enclosures:

Terminal Disclaimers for USSNs: 09/824,905; 09/825,245; 09/824,851; and 09/824,861.
Petition for Time Extension
Patent Application Fee Determination Record
Facsimile Transmittal cover sheet with deposit account withdrawal authorization.

Exhibit A
Currently Pending Claims Showing Amendments (if applicable)

–16. A set of electrophoretic probes for detecting the presence or absence of one or more of a plurality nucleotide sequences in a sample, the set comprising a plurality of probes selected from the group defined by the formula:

(D, M)-N-T

wherein:

(D, M)-N is an e-tag reporter;

D is a detection moiety;

M is a mobility modifier consisting of from 1 to 500 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron;

N is a nucleotide; and

T is an oligonucleotide specific for at least one of the plurality of nucleotide sequences, each T having a length in the range of from 12 to 60 nucleotides such that at least one nucleotide of T has a capture ligand attached;

and wherein each e-tag reporter of the plurality of probes has a distinct charge/mass ratio so that e-tag reporters of the plurality of electrophoretic probes form distinct peaks upon electrophoretic separation.

17. The set of claim 16 wherein said plurality is in the range of from 5 to 100 and wherein M is a mobility modifier consisting of from 1 to 300 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron.

18. The set of claim 17 wherein said distinct charge/mass ratio is in the range of from –0.001 to 0.5.

19. The set of claim 17 wherein D is a fluorophore, chromophore, or an electrochemical label.

20. The set according to claim 16, 17, 18, or 19 wherein said formula is D-M-N-T.

21. The set of claim 20 wherein said capture ligand is biotin.

22. The set of claim 20 wherein said oligonucleotide has at least one nuclease-resistant linkage.

23. The set of claim 20 wherein said fluorophore is a fluorescein.

24. The set of claim 20 wherein M is a mobility modifier consisting of from 2 to 100 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron.--